Note: Performing your original search, ***v-11294-a***, in PubMed will retrieve *3 citations*.

1: Br J Clin Pharmacol. 2002 Nov;54(5):478-84.

Pharmacokinetic and pharmacodynamic profile following oral administration of the phosphodiesterase (PDE)4 inhibitor V11294A in healthy volunteers.

Gale DD, Landells LJ, Spina D, Miller AJ, Smith K, Nichols T, Rotshteyn Y, Tonelli A, Lacouture P, Burch RM, Page CP, O'Connor BJ.

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AIMS: To assess the pharmacokinetic and pharmacodynamic profile of the novel PDE4 inhibitor V11294A (3-(3-cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H purine hydrochloride) in healthy male volunteers. METHODS: This was a double-blind, single dose, randomized crossover study in eight healthy volunteers who received a single oral, fasting dose of V11294A (300 mg) or placebo. Blood samples were taken before and 0.5, 1, 2, 2.5, 3, 4, 6, 9, 12, 18 and 24 h after oral dosing for determination of plasma concentrations of V11294A. Blood samples were also taken before and 3 and 24 h after dosing for the assessment of the effect of V11294A on mononuclear cell proliferation and tumour necrosis factor (TNF) release in whole blood. RESULTS: Following a single oral dose of 300 mg V11294A, plasma concentrations of V11294A and its active metabolite V10332 reached Cmax (ng ml-1; mean +/- s.d.; 1398 +/- 298, 1000 +/- 400, respectively) after 2.63 +/- 0.79 and 5.9 +/- 2.3 h, respectively. For V11294A and V10332, t1/2 were 9.7 +/- 3.9 and 9.5 +/- 1.7 h, and AUC(0, infinity) were 18100 +/- 6100 and 18600 +/- 8500 ng ml-1 h, respectively. At 3 h dosing, plasma concentrations of V11294A and V10332 (3-(3-cyclopentyloxy-4-methoxy-benzyl)-8-isopropyl-3H-purin-6-ylamine) were 1300 +/- 330 and 860 +/- 300 ng ml-1, 7 and 3 times their in vitro IC50s for inhibition of TNF release and proliferation, respectively. Treatment with V11294A resulted in a significant reduction of lipopolysaccharide (LPS)-induced TNF release at 3 h ($P < 0.001$) and at 24 h ($P < 0.05$) post ingestion. The amount of TNF released (pmol ml-1) in response to a submaximal concentration of LPS (4 ng ml-1) was not significantly altered following placebo treatment (before 681 +/- 68 vs 3 h postdose 773 +/- 109, $P = 0.27$).

In contrast, there was a significant reduction in the amount of TNF released following treatment with V11294A (before 778 +/- 87 vs 3 h postdose 566 +/- 72, P = 0.02). Phytohaemagluttinin (PHA) stimulated the incorporation of [3H]-thymidine in whole blood prior to drug administration. V11294A inhibited the PHA-induced proliferation at 3 h (P < 0.05). No adverse reactions were noted following single oral administration of V11294A. CONCLUSIONS: A single oral 300 mg dose of V11294A administered to healthy volunteers results in plasma concentrations adequate to inhibit activation of inflammatory cells ex vivo, which persists for at least 24 h without any adverse reactions.

PMID: 12445026 [PubMed - indexed for MEDLINE]

AWD 12-281

Note: Performing your original search, ***awd 12-281***, in PubMed will retrieve ***11*** citations.

1: J Pharm Pharmacol. 2003 Aug;55(8):1107-14.

AWD 12-281, a highly selective phosphodiesterase 4 inhibitor, is effective in the prevention and treatment of inflammatory reactions in a model of allergic dermatitis.

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AWD 12-281 (N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide), a phosphodiesterase 4 inhibitor, which is optimized for topical administration, was tested in a model of allergic dermatitis in mice. To obtain an allergic dermatitis, BALB/c mice were sensitized to toluene-2,4-diisocyanate (TDI). The allergic reaction was challenged by topical administration of TDI onto the mice ears. AWD 12-281 was tested for its anti-inflammatory potential by oral, intraperitoneal and topical administration. The phosphodiesterase 4 inhibitor, cilomilast (SB 207499), and/or the corticosteroid, diflorasone diacetate, were used as reference compounds. Given orally and intraperitoneally 2 h before as well as 5 and 24 h after TDI challenge, AWD 12-281 showed no, or only a transient inhibition of the allergen-induced ear swelling, whereas cilomilast significantly inhibited this ear swelling. Applied topically onto the ears before TDI challenge, AWD 12-281, cilomilast and diflorasone diacetate caused total inhibition of ear swelling 24 h after challenge, confirmed by a decrease of the pro-inflammatory cytokines interleukin-4, interleukin-6 and macrophage inhibitory protein-2. Administered topically after TDI challenge as therapeutic intervention, AWD 12-281 and diflorasone diacetate caused significant inhibition of ear swelling; cilomilast failed to do so. These results indicate that topically administered AWD 12-281 may be potent in the prevention and treatment of allergic/inflammatory skin diseases.

PMID: 12956900 [PubMed - indexed for MEDLINE]

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